

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: :  
Bernd RIEDL et al. : Group Art Unit: TO BE ASSIGNED  
Serial No.: TO BE ASSIGNED : Examiner: TO BE ASSIGNED  
Filed: January 11, 2002 :  
For:  $\omega$ -CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF  
KINASE INHIBITORS

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to examination, please amend the accompanying application as follows.

**IN THE SPECIFICATION**

Page 1, line 1, after the title insert

--Priority is claimed to provisional application Serial No. (Unassigned), filed on  
January 12, 2001.--

**IN THE CLAIMS**

Please cancel claims 1-49 and 55-67 without prejudice or disclaimer.

Please amend claims 50-59 as follows.

Claim 50. (Amended) A pharmaceutically acceptable salt of claim 69 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid;

and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 51. (Amended) A pharmaceutically acceptable salt of claim 70 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 52. (Amended) A pharmaceutically acceptable salt of claim 71 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 53. (Amended) A pharmaceutically acceptable salt of claim 72 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 54. (Amended) A pharmaceutically acceptable salt of claim 73 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Please add new claims 68-109 as follows.

--68. A pharmaceutically acceptable salt of a compound selected from the group consisting of:

*N*-(5-*tert*-butyl-2-methoxy phenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea,

*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,  
*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,  
*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;  
*N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and their pharmaceutically acceptable salts.

69. A pharmaceutically acceptable salt of the compound  
*N*-(5-*tert*-butyl-2-methoxy phenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea.

70. A pharmaceutically acceptable salt of the compound  
*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

71. A pharmaceutically acceptable salt of the compound  
*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

72. A pharmaceutically acceptable salt of the compound  
*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

73. A pharmaceutically acceptable salt of the compound  
*N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

74. A method for the treatment of a cancerous cell growth mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of a compound selected from the

group consisting of:

*N*-(5-*tert*-butyl-2-methoxy phenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea,

*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

*N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

75. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of

*N*-(5-*tert*-butyl-2-methoxy phenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea.

76. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of

*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

77. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of

*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

78. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of

*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

79. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of

*N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

80. A method as in claim 74 for the treatment of solid cancers.

81. A method as in claim 74 for the treatment of carcinomas, myleoid disorders or adenomas.

82. A method as in claim 75 for the treatment of carcinomas, myleoid disorders or adenomas.

83. A method as in claim 76 for the treatment of carcinomas, myleoid disorders or adenomas.

84. A method as in claim 77 for the treatment of carcinomas, myleoid disorders or adenomas.

85. A method as in claim 78 for the treatment of carcinomas, myleoid disorders or adenomas.

86. A method as in claim 79 for the treatment of carcinomas, myleoid disorders or adenomas.

87. A method as in claim 74 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

88. A method as in claim 75 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

89. A method as in claim 76 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

90. A method as in claim 77 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

91. A method as in claim 78 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

92. A method as in claim 79 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

93. A method as in claim 74 for the treatment of myeloid leukemia or villous colon adenomas.

94. A method as in claim 75 for the treatment of myeloid leukemia or villous colon adenomas.

95. A method as in claim 76 for the treatment of myeloid leukemia or villous colon adenomas.

96. A method as in claim 77 for the treatment of myeloid leukemia or villous colon adenomas.

97. A method as in claim 78 for the treatment of myeloid leukemia or villous colon adenomas.

98. A method as in claim 79 for the treatment of myeloid leukemia or villous colon adenomas.

99. A method as in claim 74 wherein the pharmaceutically acceptable salt

administered is selected from the group of salts consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

100. A method as in claim 75 where the pharmaceutical acceptable salt administered is the tosylate salt of

*N*-(5-tert-butyl-2-methoxy phenyl)-*N'*-(4-(4-methoxy-3-(*N*-methyl carbamoyl)phenoxy)phenyl) urea.

101. A method as in claim 76 where the pharmaceutical acceptable salt administered is the tosylate salt of

*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

102. A method as in claim 77 where the pharmaceutical acceptable salt administered is the tosylate salt of

*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

103. A method as in claim 78 where the pharmaceutical acceptable salt administered is the tosylate salt of

*N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.



104. A method as in claim 79 where the pharmaceutical acceptable salt administered is the tosylate salt of

*N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

105. A pharmaceutical acceptable salt as in claim 69 which is the tosylate salt of *N*-(5-*tert*-butyl-2-methoxy phenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea.

106. A pharmaceutical acceptable salt as in claim 70 which is the tosylate salt of *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

107. A pharmaceutical acceptable salt as in claim 71 which is the tosylate salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

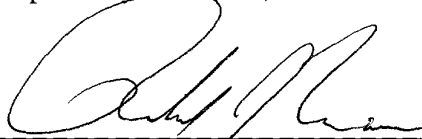
108. A pharmaceutical acceptable salt as in claim 72 which is the tosylate salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

109. A pharmaceutical acceptable salt as in claim 73 which is the tosylate salt of *N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.--

**REMARKS**

Support for new claims 68-73 and 105-109 is found in Examples numbers 5, 13, 42, 43 and 98 and page 6, lines 13-28. Methods for preparing the compounds from which the salts are derived is found on pages 57, 59, 66 and 78. Support for new claims 74-104 is found on page 2, lines 21-24 and page 11, lines 9 through page 14, line 30.

Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE CLAIMS**

Claims 1-49 and 55-67 have been canceled.

Claims 50-59 have been amended as follows.

Claim 50. (Amended) ~~A compound of claim 1 which is a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of~~ A pharmaceutically acceptable salt of claim 69 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 51. (Amended) ~~A compound of claim 2 which is a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of~~ A pharmaceutically acceptable salt of claim 70 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 52. (Amended) ~~A compound of claim 33 which is a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of A~~  
pharmaceutically acceptable salt of claim 71 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 53. (Amended) ~~A compound of claim 38 which is a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of A~~  
pharmaceutically acceptable salt of claim 72 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 54. (Amended) ~~A compound of claim 39 which is a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of A~~  
pharmaceutically acceptable salt of claim 73 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.